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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/772,467	02/06/2004	Edwin Southern	2004-0200	1112
513	7590	01/06/2009	EXAMINER	
WENDEROTH, LIND & PONACK, L.L.P. 2033 K STREET N. W. SUITE 800 WASHINGTON, DC 20006-1021			SKIBINSKY, ANNA	
ART UNIT	PAPER NUMBER			
1631				
MAIL DATE	DELIVERY MODE			
01/06/2009		PAPER		

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**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

Application Number: 10/772,467  
Filing Date: February 06, 2004  
Appellant(s): SOUTHERN, EDWIN

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Warren M. Cheek  
For Appellant

**EXAMINER'S ANSWER**

This is in response to the appeal brief filed 9/25/2008 appealing from the Office action mailed 8/23/2007.

**(1) Real Party in Interest**

A statement identifying by name the real party in interest is contained in the brief.

**(2) Related Appeals and Interferences**

There have been various judicial proceedings concerning infringement of U.S. Patent Nos. 5,700,637 and 6,054,270. There was no court decision which adversely affected the validity or enforceability of the patents. Several court proceedings might be viewed to be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. The proceedings are the following:

(1) Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 5,700,637).

(2) Oxford Gene Technology Ltd. v. Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 6,054,270).

(3) Oxford Gene Technology Ltd. v. Motorola, Inc., Civil Action No. 02-9344 before the United States District Court for the Northeastern District of Illinois (Infringement Action based upon U.S. Patent No. 6,054,270).

(4) Oxford Gene Technology Ltd. v. Telechem International, Civil Action No. 04-0013 before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 6,054,270).

(5) Oxford Gene Technology Ltd. v. Nanogen Inc., Civil Action No. 02-1687 before the United States District Court for the District of Delaware (Infringement Action based upon U.S. Patent No. 6,054,270).

There are pending reexamination proceedings concerning claims of U.S. Patent Nos. 5,700,637 and 6,054,270. U.S. Patent No. 5,700,637 is subject to reexamination in Control Nos. 90/008,429 and 90/008,844. U.S. Patent No. 6,054,270 is subject to reexamination in Control Nos. 90/008,428, 90/008,830 and 90/010,020. No final decision has been reached in these proceedings.

There are no prior or pending appeals or interferences.

**(3) Status of Claims**

The statement of the status of claims contained in the brief is correct.

**(4) Status of Amendments After Final**

An amendment after final has been filed on 11/20/2007

**(5) Summary of Claimed Subject Matter**

The summary of claimed subject matter contained in the brief is correct except for claim 22 for which Appellants state that each cell will typically include at least  $3 \times 10^{-12}$   $\mu\text{mol}$  of

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oligonucleotides (Brief, p. 9, ¶ 3). Appellants state in the footnote of page 9 that a typographical error has been made in claim 22 in that “mmol” should read “μmol”.

However, an amendment to correct this typographical error was never made. Therefore, this new limitation of “ $3 \times 10^{-12}$  μmol” was not examined as it was never recited in the claim.

Claim 22 currently recites:

Apparatus of claim 17, wherein each cell holds at least  **$3 \times 10^{-12}$  mmol** of oligonucleotide.

The claim was examined throughout prosecution history as reciting  **$3 \times 10^{-12}$  mmol** of oligonucleotide.

#### **(6) Grounds of Rejection to be Reviewed on Appeal**

The appellant’s statement of the grounds of rejection to be reviewed on appeal is correct.

#### **(7) Claims Appendix**

The copy of the appealed claims contained in the Appendix to the brief is correct.

**(8) Evidence Relied Upon**

Stavrianopoulos et al. (U.S. Patent No. 4,994,373; effective filing date of at least 9 May 1985)

Matkovich et al. (U.S. Patent No. 4,828,386; filed 19 June 1987)

**(9) Grounds of Rejection**

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 17-27 and 86-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stavrianopoulos et al. (P/N 4,994,373 claiming a priority date of 5/9/1985).and further in view of Matkovich et al. (P/N 4,828,386 claiming a priority date of 6/19/1987).
2. Stavrianopoulos et al. teach fixing single and double stranded oligonucleotide sequences to nonporous solid supports made of glass (col. 1, lines 25-41; and col. 5, lines 37-57). Stavrianopoulos teaches an array comprising predetermined sequences. For example, DNA from specific samples, such as lambda DNA (column 9, line 51) or adenovirus DNA (column 11, line 21) is used as analytes for attachment to the array. As the source of the DNA is known and pre-selected (i.e. it is not random DNA), the DNA is interpreted to be “predetermined.” Glass plates with depressions or wells (i.e. cells) are taught (col. 8, Example 1), as in claims 17, 19, 20, and 86. Oligonucleotides or oligonucleotide probe sequences (col. 5, line 58 to col. 6, line 4) are attached to the support such that oligonucleotides are able to hybridize (col. 6) thus making obvious binding the oligonucleotide via a terminal nucleotide to the support, as in claims 23 and 24. The instant limitations taught by Stavrianopoulos also apply to claims 86 and 87.

3. Further, Stavrianopoulos et al. shows use of conventional microtiter plates to contain samples (col. 12, lines 20-24), with examples that show a capacity of  $3 \times 10^{12}$  mmol of oligonucleotide, as required by claim 22.

4. Stavrianopoulos et al. teaches in situ techniques (col. 5, lines 41-46) for attaching the nucleotide sequence, as required by claim 25.

5. Regarding the limitations of claims 26, 27 it is noted that a product by process claim is examined for novelty and obviousness of the claimed product only, and that no consideration is given to the novelty or obviousness of the method of making the claimed product. See MPEP 2113.

6. Stavrianopoulos et al. teaches (col. 1, lines 29-30 and col. 5) an array of oligonucleotides with a substrate that may be plastic or glass and that various (i.e. different) polynucleotide samples may be present in the array (col. 8, lines 40-45).

7. While Stavrianopoulos et al. teaches binding of oligonucleotides or probes to a support, as set forth above, he does not explicitly teach that the binding of the oligonucleotide is covalent, as required in claims 17 and 18. Further, Stavrianopoulos et al. shows use of conventional microtiter plates to contain samples (col. 12, lines 20-24) but does not show the number of wells to be between 72 and  $1.1 \times 10^{12}$  cells as required by claim 21.

8. Matkovich et al. teaches covalent binding of a macromolecular reactant to the reaction (microporous) layer by covalent binding (col. 4, line 60 to col. 5, line 1), as required in claims 17 and 86. Matkovich et al. teaches the use of a microporous membrane on top of a support (Abstract; col. 3, lines 2-33) which can be used to bind biologically active substances including

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nucleic acids (col. 6, lines 32-60). Matkovich et al. shows microtiter plates with 96 wells via an 8x12 matrix of wells (col. 1, lines 23-26).

9. It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the apparatus taught by Stavrianopoulos et al. to insert a porous membrane with covalently attached oligonucleotides, as taught by Matkovich et al. One of ordinary skill in the art would be motivated to use the oligonucleotides of Stavrianopoulos, covalently attached to a porous membrane, on top of the impermeable surface of Stavrianopoulos et al. because Matkovich et al. teach that a porous surface results in a better binding capacity of biological substances (Matkovich et al., col. 3, lines 13-19). It would have been obvious to have attached the oligonucleotide in the method of Stavrianopoulos et al. and Matkovich et al. to the support via a terminal nucleotide as suggested by Stavrianopoulos et al. where the motivation would have been to attach the nucleotide in an orientation such that it can still hybridize, as taught by Stavrianopoulos et al. (col. 5, line 36 to col. 6, line 26). It would have been further obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Stavrianopoulos et al. to use the 96 well microtiter plate of Matkovich et al. for the purpose of analyzing an array of up to 96 samples. One of ordinary skill in the art would have a reasonable expectation of success of using a porous surface with the impermeable surface of Stavrianopoulos et al., because Matkovich et al. teaches that the porous surface may be placed on top of a backing (Matkovich et al., col. 3, lines 22-28), and he teaches that reagents may be covalently attached to his microporous membranes, as set forth above (col. 4, line 60-col. 5, line 1).

### **(10) Response to Argument**

#### *A. Summary of Appellant's Position*

Appellant contends that “to rely on a reference under 35 U.S.C. 103, it must be analogous art (M.P.E.P. 2141.01(a))” further stating that “Stavrianopoulos and Matkovich are not analogous art and that one skilled in the art would not have looked to Matkovich to modify the invention of Stavrianopoulos”. Appellant states that the reasons for this is that “Stavrianopoulos deals with nucleic acid assays whereas Matkovich is explicitly concerned with antibody assays”. Thus, Appellant concludes “a skilled person starting with the DNA assay of Stavrianopoulos would not obviously have looked to the teachings of Matkovich because it was from a different technical field (antibodies vs. nucleic acids); rather they would have looked within their own field dealing with nucleic acid assays” (Brief p. 12, ¶3 to p. 13, ¶1).

#### *B. Appellant's Arguments*

##### *In regard to claim 17*

A. Appellants argue that Stavrianopoulos et al. and Matkovich et al. are nonanalogous art and that “even if the skilled person had turned to the antibody field, they would not have modified the Stavrianopoulos apparatus in the manner suggested by the examiner”. Appellants state that motivation for using a porous membrane as taught by Matkovich et al. on top of the impermeable surface of Stavrianopoulos to bind biological substances runs contrary to the explicit teachings of Stavrianopoulos who teach that porous support materials are “less desirable for practice of the method of the present invention” (Brief, p. 13, ¶2).

B. Appellants argue that claim 17 requires the apparatus to include "an array of oligonucleotides with predetermined sequences" and that the immobilized sequences in Stavrianopoulos are unknown.

C. Appellants argue that Stavrianopoulos fails to teach or suggest an "array comprises at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell", as recited in claim 17 (Brief, p. 16, ¶3-5).

*In regard to claims 23 and 86*

D. Applicants argue that Stavrianopoulos in view of Matkovich et al. do not teach a covalent attachment of oligonucleotides to the porous material, as recited in claims 23 and 86 (Brief, p. 17, ¶2-5).

*In regard to claims 24 and 87*

E. Applicants argue that Stavrianopoulos et al. in view of Matkovich et al. do not teach that oligonucleotides are covalently attached by a terminal nucleotide, as recited in claims 24 and 87 (Brief, p. 19, ¶2-5).

*In regard to claim 25*

F. Applicants argue that Stavrianopoulos et al. does not teach that oligonucleotides are synthesized *in situ* (Brief, p. 20-21<sup>m</sup> connecting paragraph).

*Response to Arguments*

A. In response to applicant's argument that Stavrianopoulos et al. and Matkovich et al. are nonanalogous art, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed

invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). Stavrianopoulos et al. and Matkovich et al. are analogous art pertaining to the field of attaching macromolecules to a substrate. In the case of Stavrianopoulos et al., the macromolecule is an oligonucleotide attached to an impermeable substrate while Matkovich et al. teaches the covalent attachment of various macromolecules including nucleic acids to a microporous surface (Matkovich et al., col. 6, lines 32-60, specifically at line 60). In this case, Appellant's argument that Stavrianopoulos et al. teaches away from the use of a porous surface such as that taught by Matkovich et al. the argument is not persuasive because the teaching of Stavrianopoulos et al. actually suggests the option of using a porous material to bind polynucleotides. At col. 5, lines 46-52, to which Appellants point, Stavrianopoulos et al. teaches "It is preferred that the solid support to which the analyte is fixed be non-porous and transparent, such as glass, or alternatively, plastic, polystyrene, polyethylene, dextran, polypropylene and the like. **Conventional porous materials, e.g., nitrocellulose filters**, although less desirable for practice of the method of the present invention, **may also be employed as a support.**" Emphasis added by the examiner. Matkovich et al. teaches the use of a microporous membrane on top of a support (Abstract; col. 3, lines 2-33) which can be used to bind biologically active substances including not only antibodies (col. 6, line 55), but also other biological macromolecules such as proteins, receptors, and nucleic acids (col. 6, lines 32-60, specifically at line 60). Furthermore, Matkovich et al. also teach that macromolecules, such as those listed in column 6, may be attached via covalent binding of to the reaction layer (col. 4, line 60 to col. 5, line 1). Matkovich et al. provides motivation to combine the porous materials with the glass surface array of Stavrianopoulos et al. by teaching that a porous surface results in a better binding capacity of biological substances

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(Matkovich et al., col. 3, lines 13-19). One of skill in the art would reasonably have expected that the porous material as taught by Matkovich et al. would be capable of binding nucleic acids, as Matkovich teaches that nucleic acids are one of the macromolecules that may be used in his method. It would have been obvious to one of skill in the art to place the porous material as taught by Matkovich et al. on top of a backing such an array surface because Matkovich et al. teach that the porous material may be placed on top of a backing (Matkovich et al., col. 3, lines 22-28). Thus, both the teaching of Stavrianopoulos et al. and Matkovich motivate one of skill in the art to covalently attach the oligonucleotides of Stavrianopoulos et al. to a porous surface such as the membrane of Matkovich inserted into wells of a 96 well plate.

**B.** In response, to Appellant's argument that the claims require a "predetermined sequence", by which they mean a known sequence, the instant specification does not provide a specific definition for the term "predetermined" such that the claimed sequence must be a "known sequence" or a sequence whose base composition is known.

The instant specification, at page 4, provides the heading ANALYSIS OF A PREDETERMINED SEQUENCE. The paragraph that follows describes the detection of single base changes in the beta globin gene leading to sickle cell anemia. The specification goes on the state that there is a need to extend the approach to genes in which there may be a number of mutations leading to a phenotype, for example the DMD gene and the HPRT gene. The specification then describes how any known sequence can be presented completely as a set of overlapping oligonucleotides etc. (page 4, line 17). The size of a set may be N such that  $s+1=N$ , where N is the length of the sequence and s is the length of an oligomer. The instant specification, however, does not equate predetermined sequence, as is instantly claimed, with

known sequence. With regard to a predetermined sequence, one can reasonably interpret "predetermined" to include a sequence that is from a certain tissue type or cell line. Therefore, it is "predetermined" what will be arrayed. However, a "predetermined" sequence is not necessarily "known" (i.e. the base sequence composition is not "known"). The teachings in Stavrianopoulos et al. wherein DNA from specific samples, such as lambda DNA (column 9, line 51) or adenovirus DNA (column 11, line 21) are used as analytes for attachment to the array meets the instant claim limitations since these are "predetermined" DNA sequences taken from known/preselected samples. Furthermore, the description by Stavrianopoulos et al. of "various" single stranded analytes for use in an array for hybridization is reasonably interpreted as being different oligonucleotides and therefore, they also meet the limitation of having been "predetermined".

In regard to the prosecution history of US Patent Nos. 5,700,637 and 6,054,270, Appellant is kindly reminded that each application is treated on its own merits.

C. In response to Appellant's argument that Stavrianopoulos et al. does not teach an "array comprised at least two defined cells, the sequence of the oligonucleotides of a first cell is different from the sequence of the oligonucleotides of a second cell", it is reiterated that the DNA of the Stavrianopoulos et al. invention is taken from different samples such as lambda DNA (column 9, line 51) or adenovirus DNA (column 11, line 21). Therefore Stavrianopoulos et al. fairly teaches at least two different sequences. Stavrianopoulos et al. also teaches "an array of depressions or wells" for the depositing of the different samples of sequences. Therefore Stavrianopoulos et al. fairly teaches an array comprising at least two defined cells.

Further, the description by Stavrianopoulos et al. of “various” single stranded analytes for use in an array for hybridization is reasonably interpreted as being oligonucleotides that are different (col. 5, lines 37-39). Applicant has provided no evidence as to why this position is “untenable”.

D. In response to Appellant’s argument that Stavrianopoulos et al. does not teach that oligonucleotides are covalently attached to the porous material, it is noted that Stavrianopoulos et al. teaches treatment of the array with a silane linker (the amma-aminopropyltriethoxysilane of Example 1), wherein such linkers may be used for covalent attachment of DNA. However, as Stavrianopoulos does not EXPLICITLY teach that his silane linkers are used for covalent attachment, it is noted that Matkovich et al. does explicitly teach that oligomers of various kinds may be covalently attached to his microporous surfaces (col.4 ,line 60-col. 5, line 1). It is noted that appellant admits on page 17 of the Appeal Brief that Matkovich et al. teaches that reactants of different chemical properties such as ionic, molecular or macromolecular in nature (e.g. oligonucleotides as taught at col. 6 of Matkovich et al.), "may be immobilized on the reaction layer by strong physical forces or by being bonded in some manner **such as covalent chemical coupling to the surface of the reaction layer**". Emphasis added by examiner. In response to appellant’s argument that the examiner has provided “no justification” for choosing this type of attachment, it is noted that only two specific types of attachment are taught by Matkovich. As a covalent attachment is well known in the art to be a very stable attachment, it would have been obvious to anyone of skill in the art to choose this type of attachment from the two taught by Matkovich et al.

E. While it is admitted that Stavrianopoulos et al. does not explicitly teach attachment via a terminal nucleotide, the Examiner maintains that Stavrianopoulos et al. suggests such an attachment where he teaches that oligonucleotides are attached such that they can still hybridize. This teaching encompasses attachment via a terminal nucleotide. Matkovich et al. teaches covalent attachment. For the reasons set forth above, examiner maintains that Stavrianopoulos et al. in view of Matkovich et al. makes obvious the limitation of claim 24.

F. In response to Appellant's argument that Stavrianopoulos et al. does not teach that oligonucleotides are synthesized *in situ*, Stavrianopoulos et al. teach *in situ* techniques (col. 5, lines 41-46) for attaching the nucleotide sequence wherein the oligonucleotide exists "*in situ*" within the cell. Therefore, Stavrianopoulos et al. teaches *in situ* synthesis of oligonucleotides.

#### **(11) Related Proceeding(s) Appendix**

Decisions rendered by a court or the Board in any proceeding identified pursuant to paragraph (c)(1)(ii) are as follows:

(1) Memorandum Opinion on Claim Construction, Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware, November 5, 2000.

(2) Order on Claim Construction, Oxford Gene Technology Ltd. v. Affymetrix, Inc., Civil Action No. 99-348-JJF before the United States District Court for the District of Delaware,

November 5, 2000.

(3) Memorandum Opinion and Order on Claim Construction, Oxford Gene Technology Ltd. v.

Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 2004 WL 2211971, September 29, 2004.

(4) Opinion and Order on Motions for Summary Judgment, Oxford Gene Technology Ltd. v.

Mergen Ltd., et al., Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 345 F.Supp.2d. 444, November 19, 2004.

(5) Order on Motion for Reconsideration, Oxford Gene Technology Ltd. v. Mergen Ltd., et al.,

Civil Action No. 02-1695-KAJ before the United States District Court for the District of Delaware, 2005 WL 121797, January 7, 2005.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Anna Skibinsky, Ph.D.

Examiner

Art Unit 1631

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